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In re the application of: Smith, Douglas

Serial No.: 08/487,032

Filed: June 7, 1995

For: *NUCLEIC ACID AND AMINO ACID SEQUENCES RELATING TO HELICOBACTER PYLORI FOR DIAGNOSTICS AND THERAPEUTICS*

Attorney Docket No.: GTN-001

Group Art Unit: 1645

Examiner: V. Portner

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APPEAL BRIEF

As set forth in the Notice of Appeal filed August 1, 2001, and received by the U.S. Patent and Trademark Office on August 3, 2001, Appellant hereby appeals the final decision of the Examiner in the above-identified application rejecting the subject matter of the pending claims. Appellant respectfully requests that the Board of Patent Appeals and Interferences reverse the Examiner's rejection of the claimed subject matter.

I. REAL PARTY IN INTEREST

The real party in interest in the above-identified application is Astra Aktiebolag.

II. RELATED APPEALS AND INTERFERENCES

No other appeals or interferences are known to Appellant, Appellant's legal representative or the assignees which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 113-120, 123-125, 127-135, 149-150, 196-213, and 214-224 were pending in the application. Claims 113-120, 124-131, 134, 135, 150, 196-201, 204-211, and 213-219, were canceled and claims 123, 132, 133, 149, 220, 221, 222, 223, and 224 were amended to correct dependency in the Amendment and Response After Final Pursuant to 37 C.F.R. §1.116, which is filed on even date herewith. Accordingly, upon entry of the Amendment and Response After Final, claims 123, 132, 133, 149, 202, 203, 212, and 220-224 will be pending in the above-identified application.

All of the pending claims are on appeal and are set forth in Appendix A of this Brief.

IV. STATUS OF THE AMENDMENTS

A Notice of Appeal was filed on August 1, 2001, and received by the U.S. Patent and Trademark Office on August 3, 2001. An Amendment and Response After Final Pursuant to 37 C.F.R. §1.116, is filed on even date herewith.

In the Amendment and Response After Final Pursuant to 37 C.F.R. §1.116, claims 113-120, 124-131, 134, 135, 150, 196-201, 204-211, and 213-219, were canceled and claims 123, 132, 133, 149, 220, 221, 222, 223, and 224 were amended to correct dependency.

No other amendments after final have been filed. All other amendments have been entered.

V. SUMMARY OF THE INVENTION

Appellant's invention pertains to novel bacterial surface polypeptides from the organism *Helicobacter pylori* which have utility for diagnostic and therapeutics for *H. pylori* and other *Helicobacter* species. They can also be used to detect the presence of *H. pylori* and other *Helicobacter* species in a sample; and for use in screening compounds for the ability to interfere with the *H. pylori* life cycle or to inhibit *H. pylori* infection.

Appellant's invention pertains to isolated *H. pylori* polypeptides comprising or consisting of the amino acid sequence of SEQ ID NO:764, or portions thereof.

Appellant's invention further pertains to isolated polypeptides comprising at least 10 consecutive amino acid residues of SEQ ID NO: 764, wherein said polypeptide comprises at least one epitope recognized by a T cell receptor specific for the polypeptide set forth in SEQ ID NO:764 or wherein said polypeptide comprises at least one antigenic determinant of the polypeptide set forth in SEQ ID NO:764. In one embodiment, the polypeptide is a recombinant polypeptide. In another embodiment, the polypeptide comprises at least about 12, 16, 20, 50, or 100 consecutive amino acid residues of SEQ ID NO:764. In yet another embodiment, the polypeptide further comprises a pharmaceutically acceptable carrier. In still another embodiment the polypeptide comprises an additional amino acid sequence, *e.g.,* an *H. pylori* polypeptide sequence.

Appellant's invention further pertains to an immunogen which includes SEQ ID NO:764, or a portion thereof, in an immunogenic preparation, the immunogen being capable of eliciting an immune response specific for said *H. pylori* polypeptide, *e.g.,* a humoral response, an antibody response, or a cellular response.

Appellant's invention further pertains to vaccine compositions and methods for the protection against infection by *H. pylori*. In one embodiment, the vaccine compositions contain immunogenic surface proteins from *H. pylori,* or portion thereof, and a pharmaceutically acceptable carrier. These vaccines have therapeutic and prophylactic utilities.

VI. STATEMENT OF ISSUES PRESENTED FOR REVIEW

Appellant presents the following issues for review:

I. Whether independent claims 202, 203, and dependent claims 123, 132, 133, 149, 212, and 220-224 are unpatentable under 35 U.S.C. §101 as not being supported by a specific, substantial, or a well established utility.

II. Whether independent claims 202, 203, and dependent claims 123, 132, 133, 149, 212, and 220-224 are unpatentable under 35 U.S.C. §112, first paragraph, as not being enabled by the teachings in Appellant's specification.

The Examiner has addressed the rejection of the claims under 35 U.S.C. §101 and the rejection of the claims under 35 U.S.C. §112, first paragraph, together. As such, Appellant addresses both of these issues together in the following arguments.

VII. GROUPING OF CLAIMS

Claims 123, 132, 133, 149, 202, 203, 212, and 220-224 are Appellant's principal claims on appeal. Claim 202 is an independent claim directed to an isolated polypeptide comprising at least 10 consecutive amino acid residues of SEQ ID NO: 764, wherein the polypeptide comprises at least one epitope recognized by a T cell receptor specific for the polypeptide set forth in SEQ ID NO:764. Claim 203 is directed to an isolated polypeptide comprising at least 10 consecutive amino acid residues of SEQ ID NO: 764, wherein the polypeptide comprises at least one antigenic determinant of the polypeptide set forth in SEQ ID NO:764.

Claim 123 is directed to an isolated polypeptide of any one of claims 202-203 which is a recombinant polypeptide. Claim 132 is directed to a fusion protein comprising a polypeptide of any one of claims 202-203 and an additional amino acid sequence. Claim 133 is directed to a fusion protein of claim 132, wherein the additional amino acid sequence comprises an *H. pylori* polypeptide. Claim 149 is directed to a composition comprising a polypeptide of any one of claims 202-203 and a pharmaceutically acceptable carrier. Claim 212 is directed to a composition comprising a fusion protein of claim 132 and a pharmaceutically acceptable carrier. Claim 220 is directed to an isolated polypeptide of any one of claims 202-203 comprising at least

about 12 consecutive amino acid residues of SEQ ID NO:764. Claim 221 is directed to an isolated polypeptide of any one of claims 202-203 comprising at least about 16 consecutive amino acid residues of SEQ ID NO:764. Claim 222 is directed to an isolated polypeptide of any one of claims 202-203 comprising at least about 20 consecutive amino acid residues of SEQ ID NO:764. Claim 223 is directed to the isolated polypeptide of any one of claims 202-203 comprising at least about 50 consecutive amino acid residues of SEQ ID NO:764. Claim 224 is directed to an isolated polypeptide of any one of claims 202-203 comprising at least about 100 consecutive amino acid residues of SEQ ID NO:764.

The rejected claims do not stand or fall together for the reasons set forth below.

VIII. ARGUMENTS

Rejection of Claims 123, 132, 133, 149, 202, 203, 212, and 220-224 Under 35 U.S.C. §101 Under 35 U.S.C. and 35 U.S.C. § 112, First Paragraph

The Examiner has maintained the rejection of claims 123, 132, 133, 149, 202, 203, 212, and 220-224 under 35 U.S.C. §101 because, in the opinion of the Examiner, "the claimed invention is not supported by either a specific and substantial, a credible asserted utility, or a well established utility." In particular, the Examiner is of the opinion that

> A representative number of species for the claimed genus of polypeptides has not been described, not enabled as a diagnostic or vaccine polypeptide[s]. Just because a polypeptide is defined as a surface polypeptide, does not automatically define the polypeptide as a diagnostic or vaccine antigen. Even if the claimed invention were limited to just SEQ ID NO 764, the asserted biological activity of a polypeptide molecule is not defined by a linear sequence of amino acids.

Furthermore, the Examiner is of the opinion that

> [t]he cited references, Doig, et al (1995) and [Bina] et al (2000), supplied by applicant, compare SEQ ID NO 764 to the protein of [Bina] et al, which has

> been 'shown to be antigenic in vivo with both patient sera and specific monoclonal antibodies'. It is clear to the examiner that the antigen of [Bina] induces antibodies, these antibodies are present in patients that are still sick. The antibodies induced in vivo are not protective antibodies because infection persists. The protein of [Bina] has 250 amino acids and functions as a porin. The claimed polypeptide of SEQ ID No 764 only has 170 amino acids and no credible asserted utility. The protein of [Bina] is not defined as the same polypeptide of the instantly claimed invention, but is argues to 'correspond substantially'. The instant specification does not define SEQ ID No 764 as corresponding substantially to the protein of [Bina]. The meaning of the phrase 'corresponds substantially', with respect to SEQ ID No 764, has not been defined [in] the instant specification. The polypeptide of the invention is argued to be immunogenic and could induce antibodies which in turn could be used to identify the polypeptide, how circular reasoning defines a substantial, credible or well established utility has not been established.

Claims 123, 132, 133, 149, 202, 203, 212, and 220-224 also stand rejected under 35 U.S.C. §112, first paragraph, as, according to the Examiner, "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention."

Claim 202 is drawn to an isolated polypeptide comprising at least 10 consecutive amino acid residues of SEQ ID NO: 764, wherein said polypeptide comprises at least one epitope recognized by a T cell receptor specific for the polypeptide set forth in SEQ ID NO:764. Claim 203 is directed to an isolated polypeptide comprising at least 10 consecutive amino acid residues of SEQ ID NO: 764, wherein said polypeptide comprises at least one antigenic determinant of the polypeptide set forth in SEQ ID NO:764. Claim 123 is directed to an isolated polypeptide of any one of claims 202-203 which is a recombinant polypeptide. Claim 132 is directed to a fusion protein comprising a polypeptide of any one of claims 202-203 and an additional amino acid sequence. Claim 133 is directed to a fusion protein of claim 132, wherein the additional amino acid sequence comprises an *H. pylori* polypeptide. Claim 149 is directed to a composition comprising a polypeptide of any one of claims 202-203 and a pharmaceutically acceptable

carrier. Claim 212 is directed to a composition comprising a fusion protein of claim 132 and a pharmaceutically acceptable carrier. Claims 220, 221, 222, 223, and 224 are directed to an isolated polypeptide of any one of claims 202-203 comprising at least about 12, 16, 20, 50, or 100 consecutive amino acid residues of SEQ ID NO:764, respectively.

The present invention features a novel surface protein from the bacteria *Helicobacter pylori*. Appellant has described the chemical, physical, and biological properties of the polypeptide set forth as SEQ ID NO: 764. Appellant asserts that the polypeptides of the invention ***can be used for diagnostic and therapeutic purposes with regard to H. pylori infection; for generating antibodies; and to evaluate compounds useful as activators or inhibitors of the bacterial life cycle*** (see, for example, the specification at page 50).

Appellant maintains that the proposed utilities are specific and substantial utilities and are also credible, and thus satisfy the requirements of 35 U.S.C. §101. "An applicant need only make one credible assertion of specific utility for the claimed invention to satisfy §101 and §112." *Utility Guidelines,* page 15. A credible utility is assessed by ascertaining "whether the assertion of utility is believable to a person of ordinary skill in the art based on the totality of the evidence and reasoning provided." *Utility Guidelines,* page 17.

The specificity of the asserted utilities is based on the fact that the polypeptide set forth as SEQ ID NO:764 is a surface protein of the *H. pylori* pathogen, and, as such, is an attractive target for intervention. The significant pathologies attributed to *H. pylori* infection (*e.g.*, gastritis, peptic ulceration, gastric cancer) have made effective diagnosis, treatment and prevention desirable. Accordingly, Appellant asserts that the claimed polypeptides possess a specific and credible utility, as all polypeptides are not capable of utility for diagnostics and therapeutics for *H. pylori*.

As support of Appellant's specific proposed utilities of the claimed polypeptides,

Appellant draws the Board's attention to the fact that *H. pylori* bacterial surface polypeptides having structural and functional homology to the polypeptide set forth as SEQ ID NO: 764 have been reported as being important in the diagnosis and therapy of *H. pylori* infection (see, *e.g.*, Doig, P *et al.* (1995) J. Bacteriology 177:5447, and Bina J *et al.* (2000) J. Bacteriology 182:2370, copies of which are included herewith as Appendices C and D, respectively). Each of these publications describes members of the HOP family of molecules, bacterial porin proteins which are known to share chemical, physical and biological properties. These bacterial porin proteins are proposed to play a role in modulating the susceptibility of bacteria to antimicrobial therapy by influencing the permeability of the bacterial membrane, as well as a role in pathogenesis, *e.g.*, immunobiological activities in modifying the behavior of polymorphonuclear leukocytes and inducing the release of cytokines from human lymphocytes-monocytes. In fact, as described by Doig *et al.*, a member of this family, HopE (to which SEQ ID NO:764 corresponds substantially), has been shown to be antigenic *in vivo* as assessed by sera taken from *H. pylori*-infected individuals, and is immunologically conserved with both patient sera and specific monoclonal antibodies. The above-cited references provide extrinsic evidence of the asserted utility of the presently claimed polypeptides as useful for diagnostic and therapeutic purposes with regard to *H. pylori* infection; for generating antibodies; and to evaluate compounds useful as activators or inhibitors of the bacterial life cycle.

As further evidence of the credibility of the asserted utilities as set forth above, Appellant submits herewith, as Appendix B, a copy of the Declaration of Dr. Peter C. Doig Pursuant to 37 C.F.R. §1.132 (hereinafter "the Declaration"). The Declaration presents the results of experiments that ***corroborate the asserted utilities of the claimed invention as were originally disclosed in the instant application.***

An applicant can rebut an Examiner's rejection under 35 U.S.C. §101 using any one of the following: amendments to the claims, arguments or reasoning, ***or new evidence submitted in a Declaration under 37 C.F.R. §1.132***, or in a printed publication (*see* page 18 of the *Utility Guidelines*). The Declaration describes experiments which confirm that the claimed polypeptides, *e.g.,* SEQ ID NO:764 and fragments of at least 10 amino acids, have the ability to induce an immune response.

As set forth in the Declaration, monoclonal antibodies were produced using recombinant his-tagged HopE (full length mature sequence –11 C-terminal amino acids). The amino acid sequence of HopE used in the experiments is identical to the amino acid sequence of SEQ ID NO:764 at residues 24 through 155 of SEQ ID NO:764. Peptides were synthesized as 10-mers with an 8-amino acid overlap, with the first peptide starting at the glutamic acid residue of the mature, process protein and ELISA was performed. Mimitope analysis was able to map the epitopes of all monoclonal antibodies examined. The primary peptides that reacted with either monoclonal or polyclonal sera are shown in Table 1 of the Declaration. These peptides are present within the amino acid sequence of SEQ ID NO:764 of the instant application, as illustrated by the amino acid sequence of SEQ ID NO:764 shown as Appendix E, attached hereto. The location of each epitope is identified by bold, or italicized font, underlining, or double underlining within the sequence of SEQ ID NO:764.

Contrary to the Examiner's assertion that it is "circular reasoning" to say that the claimed polypeptides induce antibodies which in turn could be used to identify the polypeptide, Appellant respectfully submits that the immunogenicity of the claimed polypeptides, as evidenced by the results of the experiments set forth in the Declaration, supports the asserted utility of SEQ ID NO:764, and fragments thereof, as having utility as diagnostics and therapeutics with regard to *H. pylori* infection.

The Examiner is further of the opinion that

> [u]pon consideration of the arguments and the references submitted by applicant, the examiner believes that evidence has been made of record that defines portions of SEQ ID NO 764 to evidence antigenic cross reactivity with the P2 porin of Haemophilus pathogen. The existence of cross reactive epitopes would induce cross reactive antibodies which would result in a false positive diagnostic result. Therefore, applicant has made of record arguments and evidence that polypeptides of SEQ ID No 764 would not serve as a diagnostic polypeptide for H. pylori infection due to the existence of conserved portions of SEQ ID NO 764 being shared with H. influenzae, both are human pathogens. With respect to arguments made regarding evidence to how that SEQ ID No 764 is not a vaccine antigen, the examiner would like to point out the fact that Roupouli et al (1993) and HP World Wide (1991) documents have previously been made of record which show that H. pylori vaccines are in the developmental stages and are not predictable. HP World Wide cited Dunkley and Heap who found H. pylori compositions did not induce protective immunity. No showing has been made of record that indicates that the conserved portions of the H. influenza P2 porin are those portions responsible for the induction of protective immune response against Helicobacter pylori as well. Therefore, arguments that H. influenza P2 protein and Helicobacter polypeptide SEQ ID No 764 are both protective antigens are not convincing.

Appellant respectfully submits that Heap, Dunkley, and Monath do not teach that the administration of *H. pylori* antigens provide no protection. To the contrary, they claim that only gastrointestinal routes may not be effective for stimulation of protective immune response.

With respect to the use of the polypeptides of the instant invention as a diagnostic, Appellant respectfully submits that the references submitted by Appellant (Doig *et al.* (1995) *J. Bacteriology 177:5447*, and Bains *et al.* (2000) *J. Bacteriology* 182:2370) and the arguments set forth above, ***do not*** define "portions of SEQ ID NO 764 to evidence antigenic cross reactivity with the P2 porin of Haemophilus pathogen" as stated by the Examiner. As stated by the Examiner in the Final Office Action, "comparison of SEQ ID NO 764 with Haemophilus influenzae porin protein P2 (U.S. Pat. 6,153,406) shows SEQ ID NO 764 (170 amino acids)

shares **43 amino acids** with SEQ ID NO 10 (342 amino acids) ." Appellant respectfully submits that porin P2 and SEQ ID NO:764 **do not share more than 2 *consecutive* amino acids**. Moreover, as evidenced by the Declaration, monoclonal antibodies have been identified which are ***specific to SEQ ID NO:764***. Accordingly, it is the Appellant's position that the Examiner has not provided evidence of the existence of cross reactive epitopes which would induce cross reactive antibodies resulting in a false positive diagnostic result.

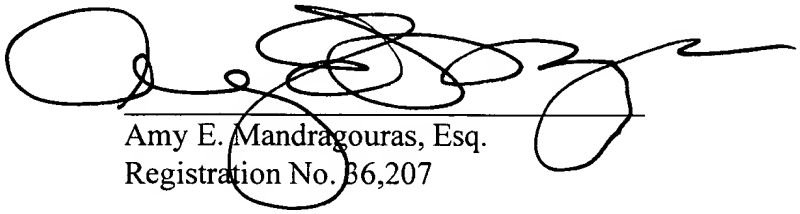
Moreover, the utilities asserted by Appellant are not "throw away" utilities (*e.g.*, use as a food supplement or cosmetic additive). Appellant must provide only one credible assertion of specific utility for any claimed invention to satisfy the utility requirement. The instant application teaches a specific and significant role for the claimed polypeptides.

Appellant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond reasonable doubt." *In re Irons*, 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Instead, evidence will be sufficient, if considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. §2164.07. In view of all the foregoing, it is evident that Appellant's invention has a *specific, substantial, and credible utility* that would have been readily apparent to one of skill in the art. Accordingly, Appellant respectfully requests reconsideration and withdrawal of the foregoing 35 U.S.C. §101 and §112, first paragraph rejections.

IX. CONCLUSION

Appellant submits that pending independent claims 202, 203, and dependent claims 123, 132, 133, 149, 212, and 220-224 are patentable and it is respectfully requested that the Board reverse the final rejection of the subject matter of these claims for the reasons given above.

Respectfully submitted,



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